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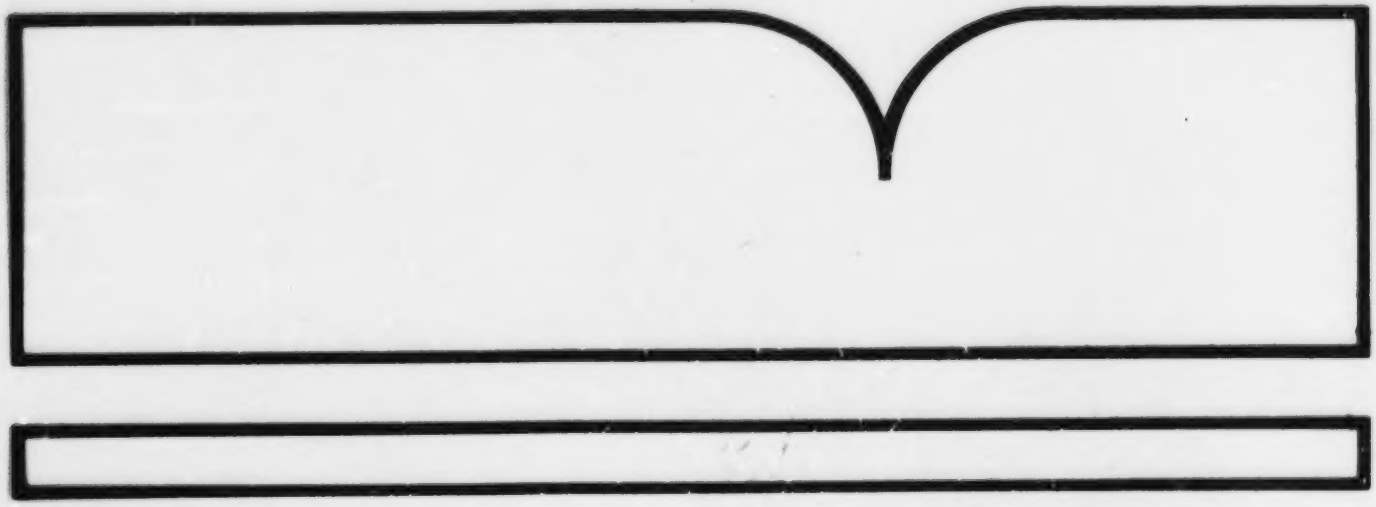

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16. ABSTRACT

This investigation assesses the ability of the heat-dissipating system of the mouse to respond to equivalent heat loads (e.g., J/g) administered at varying intensities (e.g.,J/g/s or W/kg). Use of a microwave exposure system provided a means to administer exact amounts of energy at varying rates in awake, free-moving mice. Male AJ mice were administered average heat loads of 12-13 J/g at rates of 19, 68, or 194 W/kg by exposure to 2,450 MHz microwave radiation while evaporative heat loss (EHL) was continuously monitored with dew-point hygrometry. The sensitivity of the EHL response was calculated as the heat dissipated by evaporation in response to microwave exposure divided by the heat absorbed. This ratio yields a dimensionless number that is related to the sensitivity of the EHL response and, in this study, is defined as the open loop gain (OLG) of EHL (i.e., motor response/error signal). When mice were exposed at an ambient temperature of 32.5 C to a specific absorption rate (SAR) of 19 W/kg, the OLG averaged 0.17; thus 17% of the absorved heat was dissipated by EHL and the remaining 83% of the energy was passively dissipated.

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DISTINCTION BETWEEN HEATING RATE AND TOTAL HEAT ABSORPTION IN THE MICROWAVE-EXPOSED MOUSE[1]

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This investigation assesses the ability of the heat-dissipating system of the mouse to respond to equivalent heat loads (e.g., J/g) administered at varying intensities (e.g., J/g/s or W/kg). Use of a microwave exposure system provided a means to administer exact amounts of energy at varying rates in awake, free-moving mice. Male AJ mice were administered average heat loads of 12–13 J/g at rates of 19, 68, or 194 W/kg by exposure to 2,450 MHz microwave radiation while evaporative heat loss (EHL) was continuously monitored with dew-point hygrometry. The sensitivity of the EHL response was calculated as the heat dissipated by evaporation in response to microwave exposure divided by the heat absorbed. This ratio yields a dimensionless number that is related to the sensitivity of the EHL response and, in this study, is defined as the open loop gain (OLG) of EHL (i.e., motor response/error signal). When mice were exposed at an ambient temperature of 32.5 C to a specific absorption rate (SAR) of 19 W/kg, the OLG averaged 0.17; thus 17% of the absorbed heat was dissipated by EHL and the remaining 83% of the energy was passively dissipated. Absorbing the same amount of heat but at an SAR of 68 W/kg resulted in an OLG of 0.42 and at 194 W/kg, OLG equaled 0.50. Since the OLG parameter is normalized to total heat absorption, these results demonstrate that the sensitivity of the mouse to a microwave heat load is highly dependent on the rate of energy absorption and less dependent on the total exchange of energy. The response time to microwave radiation (time required for EHL to increase to 63% above baseline) decreased as a power function with increasing SAR. These data contradict the notion that mammals have a fine control over whole-body heat exchange (i.e., thermoregulatory control) and instead support the hypothesis that the heat-dissipating system is highly influenced by the rate of temperature increase (i.e., temperature regulatory control).

INTRODUCTION

The terms "thermoregulation" and "temperature regulation" are etymologically different. The former implies the regulation of heat content, while the latter refers to the regulation of temperature in specific sites such as the rectum, skin, and hypothalamus. Snellen (1972) asserted that temperature homeostasis in man is a process of heat regulation rather than temperature regulation. Webb, Annis, and Troutman (1978) have shown in exercising humans that temperature per se is not the regulated parameter but is, rather, the end result of the control of heat loss. In a model of thermoregulatory control in humans, Houdas et al. (1973*a*, 1973*b*, 1978) concluded that the system directly exerts control over the level of heat storage and indirectly has control over body temperature.

The temperature and heat content of a tissue are physically inseparable since these parameters are directly related to each other by the mass and heat capacity of the tissue. Thus, in considering changes in the thermal state of the passive system, both heat content and temperature are regulated concomitantly. What is not understood, however, is if the sensory-motor components of body temperature control

[1] This paper has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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are as equally sensitive to total heat exchange as they are to the rate of heat exchange. In other words, does the system sense and respond similarly to heat stimuli of varying intensity (e.g., J/g/s) but of equal energy (e.g., J/g)? If the mammal is a thermoregulator, the overall motor response to a heat load should closely correlate with the absorbed heat load and be independent of intensity. If, on the other hand, the mammal is a temperature regulator, the stronger intensities should evoke greater motor responses.

The purpose of this study is to discern if the mouse thermoregulates or temperature regulates when exposed to heat loads of varying intensity. As will be explained in the Material and Methods section, the use of a microwave exposure system is ideal for this type of study since it allows for the administration of exact quantities of heat at varying rates of absorption. In this investigation evaporative heat loss is measured in mice exposed to 2,450 MHz microwave radiation at varying intensities and heat loads.

MATERIAL AND METHODS

The animals used in this study were 3-mo-old male AJ mice with a mean body weight of 24.6 ± .8 (SE) g. The mice were maintained at 22 C, 40%–50% relative humidity, and a 12 : 12 light : dark photoperiod.

ADVANTAGE OF MICROWAVE EXPOSURE FOR ADMINISTERING HEAT LOADS

The animals were subjected to the absorption of whole-body heat loads by exposure to 2,450-MHz continuous wave electromagnetic radiation inside a rectangular waveguide (5.8 × 11.2 × 30.5 cm). The schematic in figure 1 shows the path of the microwave radiation through the exposure system. When the microwaves pass through the waveguide there is a small loss in power due to leakage in the cables and electrical connections and absorption by the Plexiglas animal holder. When a mouse (or any biological material) is placed in the microwave field, a relatively large drop in power will be detected on the output side of the waveguide (i.e., P_{TRANS} in fig. 1). By measuring the incident radiation entering (P_{INC}) and leaving the waveguide (P_{TRANS}) and the power that reflects from the mouse back to the microwave generator (P_{REF}), the amount of power absorbed by the mouse can be calculated ($P_{ABS} = P_{INC} - P_{REF} - P_{TRANS}$).

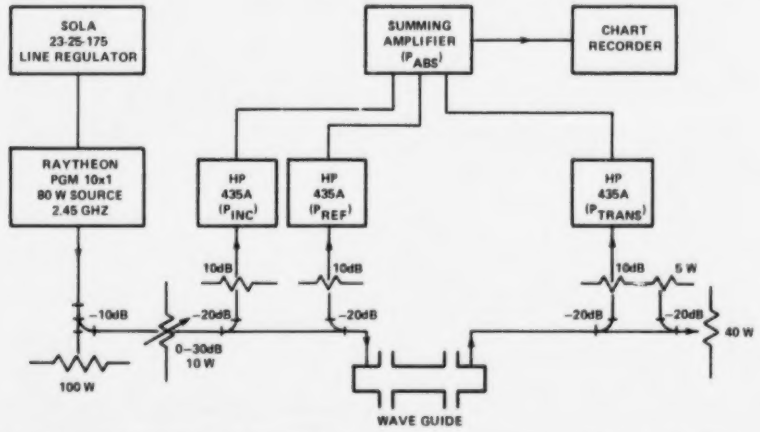

FIG. 1.—Schematic of the path of microwaves through the waveguide exposure system. Ninety percent of the power from the generator is routed to a 100-W terminal load, while the remaining power is passed through a 0–30 dB variable attenuator and then into the waveguide. Hewlett Packard 453A power meters are used to monitor the incident (P_{INC}), reflected (P_{REF}), and transmitted power (P_{TRANS}) emitting to and from the waveguide. The chart recorder monitors the absorbed power that is derived by integrating the analog voltages from the power meters. The waveguide exposure system is modified from that of Ho and Edwards (1977).

Absorbed power was continuously recorded by summing the analog voltage outputs from the power meters depicted in figure 1.

An example of the time course of absorbed power in a mouse during microwave exposure is shown in figure 2. The fluctuations in absorbed power are a result of the mouse changing position in the waveguide during exposure. For example, when oriented longitudinally with respect to the long axis of the waveguide, power absorption is maximal. Integrating the area under the curve in figure 2 (i.e., power, W/kg over time, s) yields the total heat absorbed by the animal from microwave exposure. In the example of figure 2 the specific absorption rate (SAR) is equal to 85.9 W/kg, and the exposure time is 188 s, yielding a total heat absorption equal to 16.1 J/g.

The microwave exposure system provides a way to raise the deep-body temperature at a given rate and simultaneously calculate the amount of heat absorbed by the animal. For example, consider two exposure regimes, one with an SAR of 100 W/kg over a time of 60 s and another at 10 W/kg over a time of 600 s. Both exposures result in identical heat loads to the animal (6,000 J/kg); however, an SAR of 100 W/kg will raise body temperature at approximately 10 times the rate compared with 10 W/kg. Hence the microwave exposure system permits an opportune means of distinguishing the effects of total heat exchange and the rate of temperature change on the mechanisms of temperature homeostasis.

The additional heat load accrued from the hyperthermic effect of microwave exposure could not presently be determined. The SARs of 19–194 W/kg used in this study represent heat loads of approximately two to 19 times the resting metabolic heat production of the mouse. Hence the metabolic heat load accrued from microwave exposure certainly represents a small percentage of the total heat load administered.

EXPERIMENTAL APPARATUS

The body of the waveguide, excluding the electrical connections, was immersed in a water bath thermostabilized to 32.5 ± .5 C. Two vents in the waveguide allowed for the continuous passage of air, previously dried over anhydrous calcium sulfate to a partial pressure of approximately 0.2 mmHg. The air was drawn into the waveguide at a rate of 1.2 1/min and then, via copper tubing, through a General

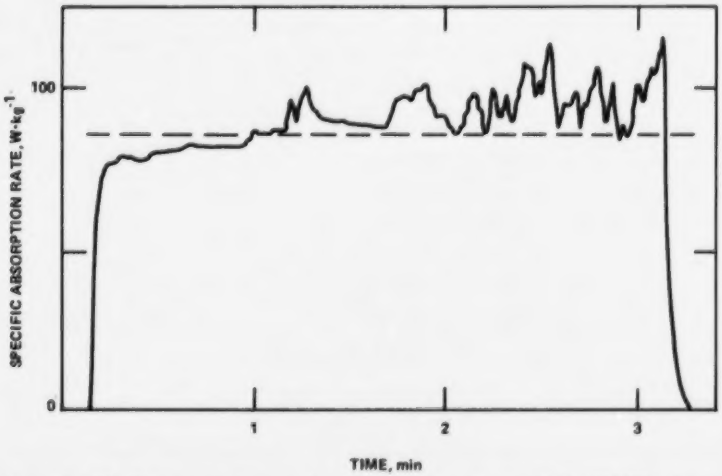

FIG. 2.—Example of the time course of power absorption by a mouse exposed to 2,450 MHz microwaves in the waveguide exposure system. The dashed line represents the average specific absorption rate (SAR) for the total time of microwave exposure. The area under the SAR curve is proportional to the total absorbed heat from the microwave source.

Eastern dew-point hygrometer sensor. Dew-point temperature was first converted to evaporative water loss (EWL) (Wood 1970) and then to evaporative heat loss (EHL) by assuming that 1.0 g of evaporated water was equivalent to 2,426 J. The analog DC voltage output from the hygrometer was continuously monitored on a chart recorder.

The mice were singly exposed in the waveguide while housed in a circular Plexiglas cage (depth, 6.7 cm; height, 3.4 cm). Mineral oil was placed beneath the cage to prevent moisture from urine and feces from entering into the water loss measurement.

EXPERIMENTAL PROTOCOL

The mice were allowed to equilibrate inside the waveguide for approximately 60 min. Equilibration was indicated by a stable EWL of approximately .05 mg/g/min. The mice were exposed to P_{INC} of 1, 3.3, or 10 W which resulted in average SARs of 19.9 ± .4, 68.4 ± 2.0, and 194.5 ± 5.4, respectively. The average exposure times were 10.1 ± .02, 3.1 ± .01, and 1.1 ± .006 min for P_{INC}'s of 1, 3.3, and 10 W, respectively. The mice were used repeatedly over a 28-day period of experimentation. Approximately four to six exposures were made over a 3–5-h period. At least 48 h elapsed between experiments on the same animal.

DATA ANALYSIS

The total amount of heat dissipated by evaporation that could be attributed to microwave exposure was taken as the integral of the rise-fall curve of evaporative heat loss (W/kg) over time. This integration (W/kg · s) yields total heat loss by evaporation per unit body weight dissipated in response to microwave exposure. It should be noted that the units of evaporated heat (J/g) are also the same for the calculation of absorbed microwave energy (e.g., fig. 2). The ratio of evaporated to absorbed heat yields a dimensionless number that describes the sensitivity of the mouse to microwave heat absorption. The higher the ratio, the greater the amount of heat dissipated by evaporation per unit heat absorbed. Using terminology from control systems analysis (Kuo 1962), if the absorbed heat is treated as an error signal by the animal and the heat loss as a motor (output) response, then the ratio of motor output to error signal is equal to the open loop gain (OLG) of the EHL system (Gordon 1982). This method of calculating OLG is similar to that used in past studies (Von Euler 1964; Stitt 1980) except that in the present study, EHL replaces rectal temperature as the motor response and whole-body absorbed heat replaces hypothalamic temperature as the error signal.

The OLG was used as a sensitivity measurement of the evaporative heat-dissipating system. The major advantage of using the OLG parameter is that it represents the response of the animal normalized to the absorbed heat load. The response time of the mouse to microwave exposure was assessed by measuring the interval between the onset of exposure and the point where EHL reached $1-1/e$ % (ca. 63%) of the total change. This time interval is defined as the time constant for the EHL system. The time for passage of air from the waveguide to the hygrometer was less than 3 s. Significant differences in OLG and time constant at the three SARs were detected by means of a t-test.

TEMPERATURE MEASUREMENTS

In separate experiments deep-body temperature was measured in restrained mice during exposure to microwave radiation. A Vitek temperature probe (model no. 101), designed to measure temperatures in a microwave field, was inserted 20–22 mm past the anal sphincter. The mice were restrained in perforated plastic tubes oriented longitudinally in the waveguide. It was necessary to restrain the animals because the waveguide construction prevented the use of conventional chronic temperature measurements in awake, freely moving animals. The mice were exposed to microwaves at P_{INC} of 1.0–10.0 W while deep-body temperature and SAR were continuously recorded. The duration of microwave exposure was usually less than 30 s.

RESULTS

Typical EWL responses of a mouse when exposed to 2,450 MHz microwaves

at an SAR of 85.9 W/kg is presented in figure 3. The area under the EWL curve, multiplied by 2,426 J/g, represents the quantity of heat dissipated by evaporation from microwave absorption. Also shown in figure 3 is the method for calculating the response time of the mouse to microwaves.

A logarithmic dose increment in P_{INC} (1.0, 3.3, and 10 W) was employed to cover an order of magnitude change in SAR (table 1). Increasing P_{INC} from 1.0 to 3.3 W caused a 3.4-fold increase in SAR, whereas increasing P_{INC} from 3.3 to 10.0 promoted a 2.8-fold increase. In spite of the large increase in SAR, the total average heat load was maintained constant by varying the exposure time.

Increasing the SAR from 19 to 68 W/kg caused a significant elevation in OLG ($P < .005$; fig. 4). An increase in SAR from 68 to 194 W/kg promoted a 19% increase in OLG; however, this difference was not significant. The relationship between OLG and SAR followed a parabolic regression curve (fig. 4). Thus, between 20 and 100 W/kg, OLG increased by 0.3 per 100 W/kg increase in SAR. Increasing SAR from 100 to 200 W/kg elicited an increase in OLG of just 0.03.

The response time of the mice to microwave radiation decreased as a power function with SAR. The time constant decreased from 9.0 ± 0.7 (SE) min at 19 W/kg to 3.8 ± 0.3 min at 68 W/kg ($P < .005$). Raising SAR from 68 to 194 W/kg caused a small, insignificant reduction in

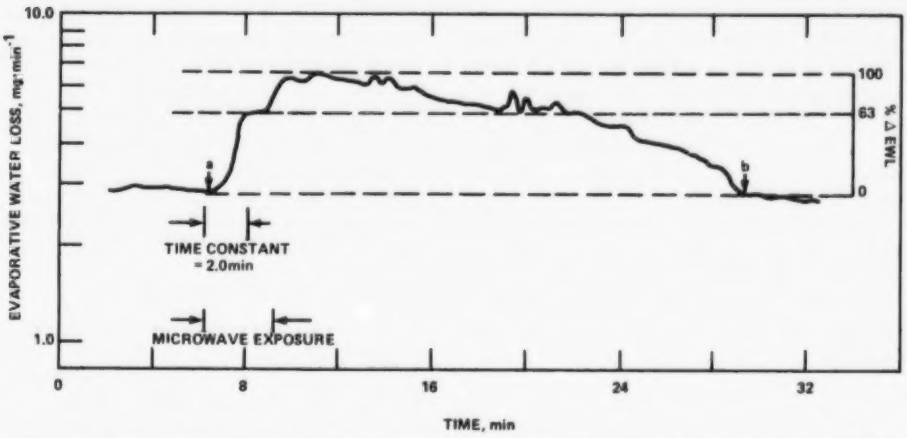

FIG. 3.—Time course of evaporative water loss during exposure to microwave radiation at a P_{INC} of 3.3 W. Area under EWL curve between points *a* and *b* represents the thermoregulatory motor response used in calculating open loop gain (OLG). Time course of microwave exposure for this example is given in detail in fig. 2. The *X*-axis on the right side is a conversion of absolute EWL to percentage change and is used for calculating the time constant (i.e., time to reach $1-1/e$ % or 63% of the change in EWL).

TABLE 1

SUMMARY OF POWER LEVEL, EXPOSURE TIME, AVERAGE HEAT LOAD, AND SPECIFIC ABSORPTION RATE (SAR) IN MICE EXPOSED TO 2,450 MHz MICROWAVE RADIATION

	Incident Power (W)		
	1	3.3	10
Heat load ($J \cdot g^{-1}$)	12.1 ± .28	12.8 ± .38	13.6 ± .38
Exposure time (min)	10.1 ± .02	3.1 ± .01	1.1 ± .006
SAR ($W \cdot kg^{-1}$)	19.9 ± .47	68.4 ± 2.0	194.5 ± 5.4
No.	26	20	24

NOTE.—Data are given as mean ± SE.

time constant (3.4 ± .4 min). The minimum and maximum time constants at all SAR ranges were 1.2 and 21.0 min, respectively.

There was a direct correlation between the rate of increase in deep-body temperature and SAR (fig. 5). Internal temperature rose abruptly with the onset of microwave exposure. Deep-body temperature increased by .0004 C/s for each W/kg elevated in SAR.

DISCUSSION

These data demonstrate that the control of evaporative heat loss in the mouse is highly sensitive to the rate of heat absorption. This conclusion is warranted by the fact that OLG increased and the response time decreased with increasing SAR. If the control system responded proportionally to the heat load and remained insensitive to the absorption rate, OLG and the response time would be the same at all SARs.

In a comparison of the OLG and time constant parameters as a function of SAR, it appears that the capacity of the mouse to sense changes in heating rate becomes saturated at extremely high SARs. From 19 to 68 W/kg, the rise in OLG and drop in time constant were both relatively steep. Increasing SAR from 68 to 194 W/kg resulted in a small, statistically insignificant increase in OLG and decrease in time constant. From figure 4 it is apparent that, at an ambient temperature of 32.5 C, OLG will not exceed 0.5–0.6. Time constant ex-

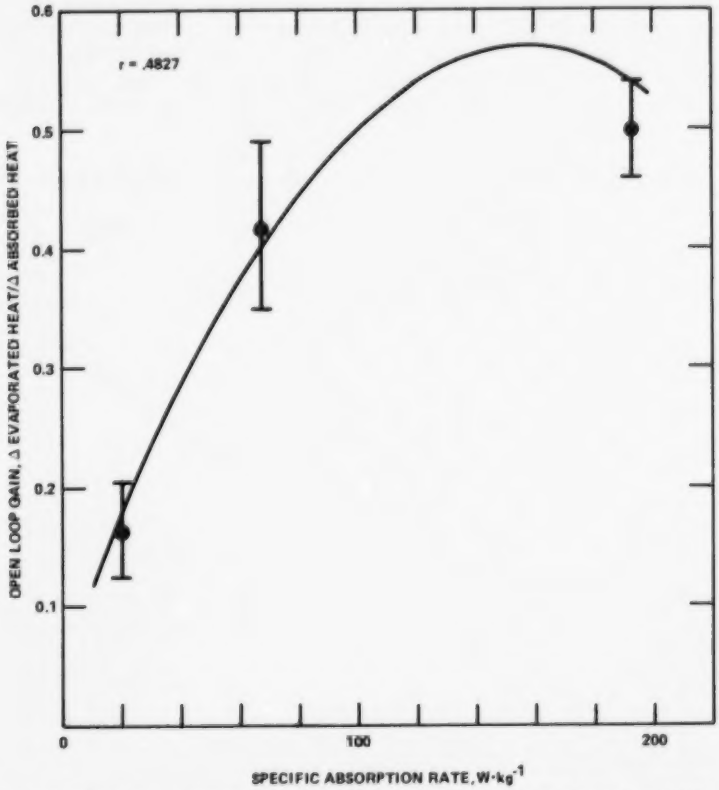

FIG. 4.—Relationship between specific absorption rate (SAR) and open loop gain (OLG) of EHL. A parabolic regression line ($Y = A + BX + CS^2$) was found to be the best fit for these data. Data plotted as mean ± SE. No. = 70 data points collected in 10 animals.

hibited saturation as a function of SAR with an asymptote of approximately 3.0 min. The change in OLG and time constant over an order of magnitude elevation in SAR demonstrate a high degree of rate sensitivity at the relatively low range of SARs. The highest SAR used in this study (194 W/kg) would rarely be encountered under natural circumstances, but the data collected at this intensity demonstrated saturability of the temperature regulatory system.

The control of body temperature in mammals is thought to be based on a "set-point mechanism" whereby the controller attempts to maintain the central and peripheral temperatures within endogenously generated set-point temperatures (Hammel 1968; Bligh 1973; Stitt 1980). Alternative hypotheses have proposed that the control of body temperature is an indirect phenomenon resulting from the regulation of whole-body heat loss (Houdas et al. 1973*a*, 1973*b*; Webb et al. 1978). Webb et al. (1978) found that oxygen consumption during exercise was closely associated with whole-body heat loss and not correlated with rectal or mean skin temperature. Since an anatomical structure for the generation of a set-point temperature has not been located, it has been argued that temperature control is achieved by a balance between integrated cold and integrated warm inputs (Snellen 1972). Moreover, a model of temperature control in man indicates that the control of deep-body temperature is an indirect result of the control of heat storage (Houdas et al. 1973*a*, 1973*b*). The fact that many tissues and organs are thermal sensitive and, when heated, can stimulate heat dissipation is strong support for a thermal exchange model rather than a one- or two-temperature set-point model (Snellen 1972). The data in the present study do not necessarily support the set-point model of temperature control, but they strongly oppose the idea that the regulatory system is driven solely by absorbed heat per se. Instead, the data indicate that the heat dissipating system of the mouse is strongly affected by the rate of heat absorption. It

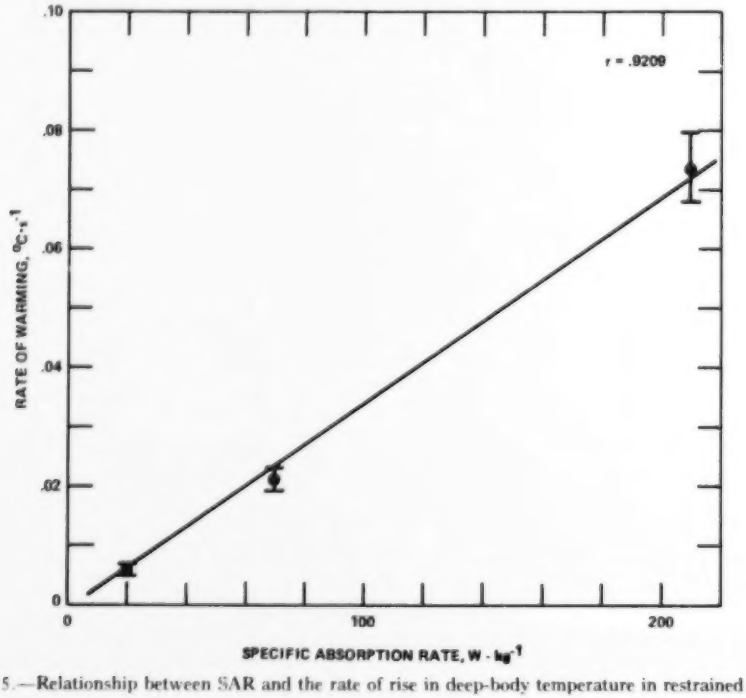

FIG. 5.—Relationship between SAR and the rate of rise in deep-body temperature in restrained mice

will be of interest to discern the characteristics of rate control in larger species.

A major problem in selecting between a model of thermoregulation and temperature regulation is that tissue temperature and heat content are irrevocably linked as demonstrated by the equation, $\Delta S = mc\Delta T$, where ΔS = change in heat content of tissue (J), m = tissue mass (g), c = tissue heat capacity (J/g/°C), and ΔT = change in tissue temperature (°C). Hence, assuming that m and c are constant, the regulation of temperature is always concomitant with the control of heat content. When average body temperature increases during heat stress, tissue heat content and, subsequently, heat loss will increase proportionately. That principal temperature measuring sites such as the rectum, skin, or hypothalamus do not correlate with the rate of heat loss does not warrant the conclusion that temperature is not regulated.

This study differs from others since it distinguishes the importance between total heat exchange and rate of heating on the activation time and sensitivity of EHL. Although only one temperature, deep body, was measured, it can be assumed that the rate of change in deep-body temperature is proportional to the change at other sites in the mouse. Elevating SAR not only increases the rate of temperature change but also increases the overall elevation in body temperature on the termination of microwave exposure. It remains to be seen if the mouse responds to the overall change in temperature or to the rate of change.

Why is the heat-dissipating system of the mouse more sensitive to the rate of heat absorption rather than to total heat exchange? It is possible that by adjusting the OLG of EHL to the rate of heating the animal may be able to anticipate potentially large thermal loads. Anticipating thermal loads may be critical for the relatively slow-response nature of the temperature regulatory system. For example, the time constant to increase EHL in response to ambient heating (Houdas et al. 1973*a*) and exercise (Chappuis, Pittet, and Jequier 1976) can take 10–20 min in humans. The data of the present study indicate that at least 60 s are required before EHL is activated in the mouse. If the temperature regulatory system could maintain a second-to-second evaluation of total body heat and evaporate the heat in the same amount of time required for absorption, a pure thermoregulatory system would be feasible. But since the activation of the heat-dissipating system is extremely slow in relation to the rate of heat absorption from the environment, it seems probable that the sensitivity of the system (i.e., the magnitude of OLG) must be, at the onset of heat exposure, adjusted to the rate of heat absorption in order to maintain a stable body temperature.

Stolwijk and Hardy (1974) contended that rate sensitivity is important in physiologic control since it strongly opposes a rapid departure of the controlled variable from the steady state. The fact that thermal receptors are highly sensitive to the rate of change in temperature (Dykes 1975; Duclaux and Kenshalo 1980) further supports the hypothesis of a rate controlled system. Wurster and McCook (1969) have demonstrated an important rate sensitivity effect of skin temperature on sweating in humans.

Heating with microwaves is clearly not a normal form of heat stress as would occur with radiant or convective heat. Microwaves permeate throughout the internal tissues, whereas the latter forms of heat act directly on the surface of the animal and indirectly heat internally by conductive and convective heat transfer. Studying thermal physiology with the waveguide technique, as was done in this study and by others (Ho and Edwards 1977), offers unique advantages because the rate and quantity of absorbed heat can be measured continuously. By directly monitoring heat absorption, we have demonstrated the effects of total and rate of heat loading on the control of evaporative heat loss.

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